IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: Heath *et al*.	Group Art Unit: 1634 Examiner: J. Goldberg
Serial No.: 09/241,636	
Filed: February 2, 1999	
For: Process for Isolating, Amplifying and Characterizing DNA	

STATEMENT OF SUBSTANCE OF INTERVIEW

Honorable Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

In response to Examiner Initiated Interview Summary dated November 5, 2005, please find below Applicants' statement of substance of interview:

During the telephonic interview, the examiner brought Dean *et al*. (Am. J. Hum. Genet. Vol. 55, pages 788-808, 1994) to Applicant's attention. Applicant presented 4 technical reasons why the lysis buffer of Dean containing 20mM Tris pH 8.0, 1% SDS and RNase A would not be combinable with the teachings of Shieh and Harvey, directed to drying a lysis reagent on a solid support. The Examiner indicated further consideration was given to the declaration filed by Dr. Dirk Loeffert discussing the ability of SDS to denature RNase.

Below are technical reasons why the lysis buffer of Dean *et al*. containing 20mM Tris pH 8.0.1% SDS and RNase A would not be combinable with the teachings of Shieh and Harvey, directed to drying a lysis reagent on a solid support:

1. The present claims are novel compared to the teaching of Dean *et al*. since Applicants claim a bind (wash-elute) procedure whereas Dean *et al* separate the liberated nucleic acid by using a phenol-chloroform method followed by precipitation.

Consequently, Dean does not even describe the presence of a solid support, much less a pre-treated solid support.

2. Applicants also do not believe Dean *et al* is relevant in terms of obviousness in terms of a combination with Shieh and Harvey. That is, in Dean *et al*., the RNase is added directly before use of the lysis buffer since otherwise the enzyme will be decomposed by the detergent. Thus, in Dean *et al*., you have a composition of SDS and RNase which is supposed to be active for only 10 minutes (the described incubation time). Afterwards Proteinase K is added which will decompose the remaining RNase as well as other proteins that may be present in the lysate. Consequently, it only has to be guaranteed in Dean that the RNase is active for 10 minutes. In contrast thereto, in the presently claimed method, the lysing reagent/enzyme combination is dried on the solid support. Since this takes some effort, you would not do it when you intend to directly use the thus treated solid support afterwards. The intended purpose is to store the thus pre-treated solid support until use. This may be a long period of time, for example, for many months. Over the entire time period, the RNA digesting enzyme remains active in the presence of the lysing reagent. That this would have been possible is not at all obvious from the teaching of Dean *et al,* as it is not required at all by Dean *et al.* that the RNase remain active in the presence of SDS for such a long time.

3. The concentration situation between the present claims and Dean *et al*. is also completely different. In Dean *et al*., SDS is present in a concentration of 1% together with RNase. Contrary thereto, according to the present claims, the lysing reagent in its entirety is dried on the solid support, *i.e.* the liquid components are removed and the solids are present on the support in their concentration. In Dean *et al*, since SDS is only present at 1%, one might expect that RNase will be only slightly decomposed during the short 10 minute incubation time. However, it could not have been expected from Dean *et al*. that if the RNA digesting enzyme is in contact with the higher concentration of lysing reagent for a long period of time, it would remain active. Furthermore, when a sample is added to the instant pre-treated solid support, the concentration of the lysing reagent present should be much higher than 1% and, thereby favor a decomposition of the RNA digesting enzyme. However, even then, the RNA digesting enzyme remains active for a period of time which is sufficient to decompose the RNA.

4. In Qiagen's PUREGENE isolation procedure RNase may optionally be used in order to obtain RNA free DNA. A copy of the handbook for PUREGENE which is publically available on Qiagen's website, is being submitted herewith. On page 7 of the handbook, it is indicated that RNase should be refrigerated for storage. This shows that RNase is heat sensitive, and consequently, intensive heating as described in Harvey may decrease the RNase activity. On the other hand, if RNase shall be used, according to the protocol on pages 19/20, the RNase is added after the lysis step (see steps 7 and 8). This indicates that commonly, one should avoid preparing and storing a lysis buffer containing RNase for a long period of time. Indeed, it is common practice to add RNase to a lysis buffer either directly before use (as in Dean *et al*) or as in the PUREGENE method, even after the lysis so as not to deteriorate the RNase activity.

Respectfully submitted,

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Date: 06 November 2009

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